From Prontolyn to Biaxin: The Half-Century of Antibiotics

J.I. Frederick Reppun MD

A leather pill kit made in 1954 at Molokai Ranch for Dr J.I.F. Reppun. The inscriptions read, "1954, Molokai, Gift of J.D. Fitzgerald, Mgr., Molokai Ranch" and "Dr J.I.F. Reppun, Kaneohe." (Photo courtesy of Hawaii Medical Library.)

I was in my third year at Harvard Medical School in 1938 and doing an externship in Boston's Children's Hospital. The patient in the ward bed was a pretty, teenage girl; I should say that she must have been pretty at one time, because her face was distorted by a massive swelling that half-closed her eyes. Her face was one of suffering but she uttered not a whimper; she couldn't talk. I was supposed to learn how to do a history and physical and this was my first patient. I went out of the ward to ask the preceptor what I should do; how could I ask her even to tell her story? He shocked me by saying she had a severe infection and would probably die soon. One so young and in the bloom of adulthood? I was assigned to another patient.

I returned the next day expecting to see that bed empty. Instead, her eyes were less swollen; they were brighter with recognition. The attending physician walked in. "Isn't it a miracle?" he said as he radiated the joy of it. "We've been given a small amount of Prontolyn," he explained, "and we've been giving it to her in liquid form by mouth every 4 hours. Have you heard of sulfanilamide?"

We students had heard inklings of a new compound being developed by the faculty physicians of the Harvard service but it was being laboratory-animal-tested and wouldn't be available in the near future.

The young woman recovered. I can still see her face in my mind's eye, more than half a century later.

Infection was our chief enemy in those days, we neophytes were taught. Not only were we instructed in asepsis, we were drilled and drilled again. The nurses in charge of operating

rooms and delivery rooms acted like military drill sergeants as we tried not to miss a single step as we scrubbed until our hands and forearms were almost raw; as we learned to be automatons in using elbows and knees to turn off the water faucets, and dry with sterile towels; as we were careful not to rub our noses before thrusting arms into sterile gowns and then into rubber gloves. One little slip in technique, hardly noticeable but immediately picked up by the sharp-eyed nurse, and back to the scrub-sink we had to go and start the routine all over again.

I had the advantage of my physician father's tale about Lister's solution. It had come out in his day, somewhere in the early 1900s. As an apprentice to a surgeon in a hospital in Moscow (my father's education and training took place all over Europe—in Germany, Austria, Riga, and Moscow), Papa noticed that the surgeon made much of the newest and best technique: Soaking his hands in the strong solution of phenolic acid, and then picking up a scalpel with his bare hands, and making the incision. However, that surgeon was more show than substance. After picking up the scalpel, he reached up with his *sterilized* other hand, grabbed the dirty handle of the skylight, and adjusted it to his liking, and then applied the scalpel!

In my learning days, our hands were better treated with Zephiran solution, a mercurial, but not much better; and, we wore rubber gloves.

The Moscow operating room had no electric operating light; the room was built so as to have panels in the roof to admit light. In those climes it had to be built with a southern exposure. Even so, an artificial operating light was needed: An oil lamp that had a highly polished brass parabolic mirror in back of it that reflected a beam horizontally across the room. The surgeon, like nearly every doctor in my father's day, was helpless without the head mirror, through a hole in the center of which one eye could see what blood vessel he needed to tie off quickly, even if it meant twisting his neck till it hurt, just to focus that reflected light on what he was trying to do.

Asepsis? Hardly! The surgeon was to be forgiven if he, without thinking, reached up with a bare hand to adjust the head mirror. Or the skylight, for that matter. What with no air conditioning in those days, the skylight admitted a breeze as well as light. The poor surgeon, sweating as he tried to find that pulsating artery, needed the breeze desperately, or the sweat from his forehead would obscure his vision, or much worse drop into the operative field.

Why did I choose to go into medicine? Well, my European-trained father was a general practitioner and surgeon in Honolulu, but he did not talk to me about following in his footsteps. I did visit him in his office in the Alexander Young Building during my high school years at Punahou, but I did not observe him at work beyond the door of the waiting room where I sat and waited for him and talked to Miss Mildred Suehiro, his girl-Friday. What we knew of his work then and earlier was that he was often away from home and missed meals with us. When we were younger, living in Kahaluu, my two younger brothers, mother, and I would not infrequently ride with him to Queen's in Honolulu, and sit in our car, the first model of a Chevrolet touring car, while he made evening or Sunday rounds. If anything, this and the rest should have soured me on being a doctor as a profession, because we would often have to spend hours in the car, waiting for him, so we could go home to bed, well past midnight. We kids would have worn ourselves out racing around the Royal Palm oval and lawn in front of the old, pyramidal-stair entrance to Pauahi.

As I remember, I never even thought about a job or a profession as I entered Harvard College; I was interested in learning everything. For my electives, I chose anthropology, geology, music appreciation, history, and art. I did not have to major, but chose to go for a BS rather than a BA. Pre-med? No such thing. The comparative anatomy course fascinated me and I was tempted by its Professor Rand, who was also my tutor in my second and third years, to go into that field of research. His influence on me was great, often as a counselor in general.

Summers I had a job at Woods Hole on Cape Cod as an assistant to my father's good friend and fellow refugee from Russia, Paul Simon Galtsoff, scientist and chief of the U.S. Bureau of Fisheries Laboratory there. He and his wife Genia were my surrogate parents (it wasn't so easy to go home to Hawaii during vacations in those days!). Galtsoff was doing research on the sex life of the oyster, *Ostrea virginica*, and I was his assistant—thereby deep into science but with no relationship to medicine.

My roommate in Lowell House and my best friend, to whose family in Rochester, New York, I would often repair during holidays, applied to Columbia P and S in his third year and was surprised that he was accepted. He asked me to do the same. I wasn't interested in going to New York City, but I did apply to Harvard Medical School, sort of casually and with no further thought about it as time went by. I did have one interview with Admissions Dean Pennypacker, a very friendly but probing old man who treated me to lunch in the faculty dining room.

Flabbergasted is the correct word for the way it struck me when a letter arrived from the dean, saying that I had been accepted, provided I paid $50. My roomie, Bob Robinson, cheered (he later became professor of orthopedics and chief of the department at Johns Hopkins). I just didn't know what to do. Instead of tossing a coin, I sent my father a telegram (no phones to Hawaii in those days): IF YOU WANT ME TO GO TO MED SCHOOL SEND ME $50 STOP. I figured I'd leave it up to him to make the decision, and he did, he wired me the $50!

Going back to that third year at HMS, we neophytes, having successfully delivered 12 babies NSD-OA (normal spontaneous delivery-occiput anterior) of their mothers at the Boston Lying-in under the critical eyes of chief residents supervised by famous chief Frederick Irving MD, went out *on district*. We were sent in pairs to any one of several outreach houses belonging to the medical school, in outlying areas of Boston where the poor lived. For two weeks we lived there and, by turns, waiting for and dreading the telephone call that meant one of us had to respond by going to the home of the parturient woman and do the home delivery. We were lucky if a public health nurse was there, waiting to assist, actually to take charge.

I was not that lucky. My first call was to a black family, a *multigravida* in labor who was in full control of herself and quite tolerant of the learning physician who had come to preside at an accouchement that did not need him at all (patients had been screened: No *primigravida*, no complication of pregnancy, no unusual presentations). I was nervous and fumbling. We were not allowed to do vaginal examinations and to do a gloved rectal digital was not very revealing of what was transpiring to us who had no wealth of experience behind us as yet.

The kit we carried with us contained a copper oblong box with lid into which we were to pour water, insert the rubber gloves, the scissors with which to cut the umbilical cord and the ribbon-tape with which to tie the cord. This was to be given to someone to

take to the kitchen and be put on the stove; it was to be boiled for 20 minutes.

Meanwhile the parturient mother in active labor was to place herself across the bed with her buttocks at the edge. Her two legs, flexed at hips and knees and spread open, were anchored by her feet, each on one of two chairs at bedside separated far enough apart for the accoucheur to sit on a third chair in between and face the exposed perineum. For the sake of privacy, a clean white sheet was spread over her legs to make a tent within which I was to do my job. I was also to be given a basin of clean soapy water with which to bathe that presenting private part.

However, time was not on my side. The baby was in a hurry to exit. Rather, it was the mother who had the control. She asked me if I was finally ready, but spared me the word *finally*. I said I was, as they brought me the copper tin of boiled gloves. Boiled, did I say? As I opened it and tried to take out a glove, it was still boiling! The mother was pushing. The head was crowning. As I was desperately struggling to put on the hot gloves, the assembled multitude: Grandma, aunty, and the older children all rushed out of the room because the kitchen stove had exploded. They screamed as they abandoned me completely. I discarded all etiquette and my careful training. With one glove half on, I used both hands, the other bare, to cup the baby's head as out popped a fat little brown girl. We weren't supposed to do episiotomies; and there certainly wasn't any need for one, nor a tear, nor even a need for my presence. The mother looked at me and smiled benignly. The gang came rushing back and watched as I tied the cord fairly expertly next to the umbilicus and then severed it proximately.

The placenta expelled itself as if it too wanted out in a hurry. In those days we had been taught to milk the blood in the cord back into the baby before tying the cord. Not until years later when I was solo on Molokai did I figure out on my own that the cord was pulsating with the baby's heartbeat (the placenta already separating from the uterine wall and not being squeezed by the uterus in its flaccid state immediately postpartum). To milk the cord toward the infant was to contravert the natural state; no wonder so many infants hemolized their overload and turned a bit yellow!

The placenta was handed to the father hovering in the background, who knew from past experience that it was to be buried in the backyard near a tree.

One of my classmates got himself into a donnybrook with the city, and with the medical school, when his first on district delivery turned out to be stillborn, and he casually told its father to bury it in the backyard, placenta and all.

Asepsis? Hardly, but the germs weren't as lethal or as much around as they are nowdays, I expect.

That summer, on vacation at my betrothed's in western Pennsylvania, at a large family picnic, her physician uncle, an elderly solo country doctor, asked me if I would like to accompany him into the house to examine a young woman relative who had gone into labor and had excused herself from the gathering. I was struck dumb when he did so, *per vaginam* with his bare hand (after he had washed it with soap and water) and without any antiseptic. When I explained to him that we had not been taught that way, he just laughed and did not insist that I examine her too, as he had suggested at first.

Jean, my bride that summer, about to teach biology at Carnegie Tech that fall after getting her Masters from Columbia, said she had accompanied Uncle Doc to many home deliveries and had assisted him. He confided in me how once he had delivered a farm woman at her home while the father stood in the doorway with a shotgun on his arm "Doc," the man threatened, "If that baby don't come out right, I'm a goin' to git ya." That was long before the lawyers got into the picture; the shotgun was more effective than an insurance premium. Obviously, Uncle Doc was unperturbed. He finally quit practicing at 95, and he was never sued.

The summer before my last year at HMS, I had a personal experience with sepsis. It taught me two things: (a) the importance of *primum non nocere*, and (b) to be sensitive to the patient's pain as if it were my own.

At *pau hana* at the Bureau of Fisheries in Woods Hole, I was using the electric buzz saw in the basement workshop and carelessly got my left index finger into the blade of the toothed saw. It nearly severed the distal phalanx. I was rushed by car 25 miles to the hospital in the center of Cape Cod, and placed supine on the operating room table. The OR nurse took off the bloody first-aid bandage and doused the finger with Tr. Iodine straight out of the stock bottle. I nearly leaped out through the skylight. The doctor walked in as the nurse draped the hand. He gave me a local block with novocaine and proceeded to stitch up the wound.

Of course, it became infected—the iodine traumatized healthy tissues more than the buzz saw had. I'll never forget the weeks and weeks of frequent visits to the doctor's office in Falmouth and the pain of the *proud flesh* that erupted as a consequence of sepsis. No oral or topical antibiotics were used at that time. Finally it healed, *per secundum*, the distal phalanx slightly askew but functional. Proud flesh is exquisitely tender, I learned first hand.

Always thereafter every patient of mine who had a nail poke or a laceration that required debridement and sutures, was first washed gently with soap and water (preferably pHisoHex), then infiltrated with 0.5% xylocaine into the wound, directed subcutaneously and not through the skin, then explored, debrided, doused with pHisoHex thoroughly before actually suturing, with bare hands (I can document that no wounds so treated in the office the past 50 years got infected).

A collateral confirmation: I assisted at major surgery on nearly all my patients and soon decided who was the best surgeon with the best outcomes. I remember only two who were the most gentle with raw tissues within the body's integument. Natural tissues resist infection; traumatized tissues are vulnerable to the onslaught of bacteria that are ever present despite the most stringent asepsis, and perhaps because of the hard scrubbing that goes on.

My fourth year at HMS Jean and I were separated by distance, but we kept the postoffice busy. There were no electronics, no phone calls, and no air travel. Infrequent long weekends and vacations meant traveling with a classmate in a model-A Ford over devious wintry roads (no freeways). She was teaching in Pittsburgh.

After graduation in June 1939, being penniless but supported by a working wife, I did not aspire to an internship at Boston City or at Mass General. Instead, I was accepted at Pittsburgh Medical Center, a 3-hospital complex. Graduation had been punctuated by a close friend and classmate who almost handed back his diploma because his first name, James, was emblazoned as Jacobus. What upset him, a mid-westerner, was that he thought it was Jewish; he had no Latin in his pre-med.

I was handsomely paid $20 a month *to cover cigarettes and laundry*. However, Jean and I lived with her folks and my whites were laundered with theirs. That saved us a lot because in those days a drawer opened to take out a white shirt usually revealed soot already smearing it. As for smoking cigarettes, unlike my three colleagues in first year anatomy, I never could figure out the rationale of using two fingers pickled in, and stinking of, formaldehyde, to take out a cigarette and place it between one's lips. In college, at a formal, white-tie dinner as guest of the house master Lawrence Abbot Lowell, a mandated, after-dinner Cuban cigar did me in for 48 precious hours. Never again!

A two-year general residency in medicine, ob-gyn, and pediatrics at Sewickly Valley General Hospital was cut short in 1941 (the surgery part) by the imminence of the war and the *invitation* I received in the mail to come serve my country for a year as a medical officer in the military, courtesy of President Franklin Roosevelt.

Infections? The sulfa drugs had progressed from sulfanilamide to sulfapyridine and to sulfathoxizole all of which made a lot of patients sicker than before. The pneumonias were invariably hospitalized for 10 or more days. We were hearing of the Trueta treatment of compound fractures by irrigation, debridement, salting with sulfa and then sealing in a plaster cast and allowing maggots to do their job on the laudable pus.

In October of 1941, as first lieutenant MC AUS, I was for a brief stint at Fort Belvoir in Virginia giving immunizations to raw recruits as they filed between two of us medical officers. Medics caught the few who fainted afterward and helped them to empty cots.

Jean and I were blissfully living an 8 to 4 existence in a cute cottage outside the sprawling army base. Late in the afternoon of December 7, we drove through the front gate to visit the PX. The sky was dark to the west, with visible lightning and distant thunder. My answering salute to the guard at the gate was still awkward, especially as I had to switch hands on the steering wheel in order to do so. We had heard on the radio the first shocking news about Pearl Harbor and the heavens to the west seemed to confirm it was the dark clouds of war that approached us. Next day Jean visited Hawaii Delegate to Congress Samuel Wilder King and was reassured that my family in Hawaii was safe. King gave her a pass to the gallery and she heard Roosevelt declare war on Japan.

A month later the wrenching tearing away from my beloved as I boarded a transport at Brooklyn Naval Yard was shared by a multitude of other GIs and officers. We even tried to get an officer married just before he kissed his betrothed good-bye. "Miceli!" the master sergeant roared out amid the turmoil. "Answer with your first name as you step on the gangplank." "Joseph," came the answer as the clinch tore apart.

We all had overcoats and long-johns based on the rumor we were to go to Iceland. Instead, the convoy of seven ships steamed south and through the Panama Canal, thence to Australia. We soon discovered that we were the 9th Station Hospital, a 250-bed unit with 30 regular army nurses aboard, bound for New Caledonia.

Shortly after arrival at Noumea and during the bivouac at Paita, I became a victim of another medical experience, the result of which *trained* me even more deeply as a physician by reason of making me a patient first. I developed a lobar pneumonia, during 10 days of which I had total amnesia of a delirium state. Without benefit of x-rays (our unit had been smashed when unloaded onto the dock) and no intravenous fluids, I was treated by my colleagues and by dedicated nurses around the clock in an empty 40-bed ward tent that was left behind for my sake as the unit moved up the island farther north. I was in a hand-crank hospital bed, in an old oxygen tent powered by a small generator, supplied with ice to cool the oxygen. The ice was requisitioned or rather cajoled by two colleagues who boarded a ship in Noumea. They were caught in the act by the division surgeon, who helped in the pilfering. The new sulfapyridine was given to me by mouth; it made me sicker, but I credit the nurses and my fellow doctors for pulling me through, rather than the sulfa (to which I have been allergic ever since).

Convalescence took 6 weeks, during which time dragged on and depression set in; there was no Prozac available then. The illness and the sequelae made me a better physician, I swear. However, I will never again let a kind nurse shave me with a dull razor!

During my convalescence, near its end, the cot next to mine in the ward tent became occupied by our dentist. He had an ischiorectal abscess that was causing him great pain. Sure of the diagnosis, the surgeon elected to drain it at bedside (I do not remember whether it was so decided to save the OR tent from being contaminated by *E. Coli* and staphyloccocus, or whether the OR tent was not set up yet). I had a ringside seat as Joe Phyllips, the surgeon, with nurses and assistants hovering around, opened up an ampoule of a brand-new anesthetic—Pentothal—just arrived. He filled a large glass syringe and attached a 20 gauge needle which he inserted into a vein. Bruggle was in the left lateral decubitus position, his *okole* prepped and draped and right in front of me. Joe told his patient to start counting out loud as he slowly pressed in the plunger: "One, two, three," Bruggie kept counting. When he got to 80, Joe gave up waiting. He grabbed the scalpel and made a deep incision; the pus poured out, overflowing the basin. Joe packed the incision open with yards of lodoform gauze, inserted it deep into the abscess cavity. Bruggie: "90, 91, 92" finally woke up and asked "When are you going to start, Joe?" He was unaware that it was over. That might have been the beginning of the same-day surgery now in vogue.

In 1994, I, a captain MC AUS, was the receiving medical officer at the 9th Station Hospital on the beach not far from the Matanikau river on Guadalcanal. The island had been secured prior to our move from New Caledonia, but there were still occasional air-raid alarms as the Japanese forces were being gradually pushed out of Munda, an island of the Solomons to the northwest of us. Proof of such safety was that we had a new batch of nurses' quarters within a double barbed-wire stockade, not to keep them in but to keep out the rapacious officers and enlisted men. I was the last one of Task Force 6814-Q that left Brooklyn Navy Yard in January 1942 to be rotated home after two and a half years overseas.

The surgeons had a GI in a ward bed with a badly infected GSW wound and compound fracture of his forearm. Our whole staff was excited because we had requisitioned—and lo and behold—received several large syringes full of penicillin in oil, 5 cc each, to be given deep into the gluteal region of the soldier. We had heard about it, but had never expected to get the new *wonder drug*. The soldier recovered enough to make it back to The States by air-evac.

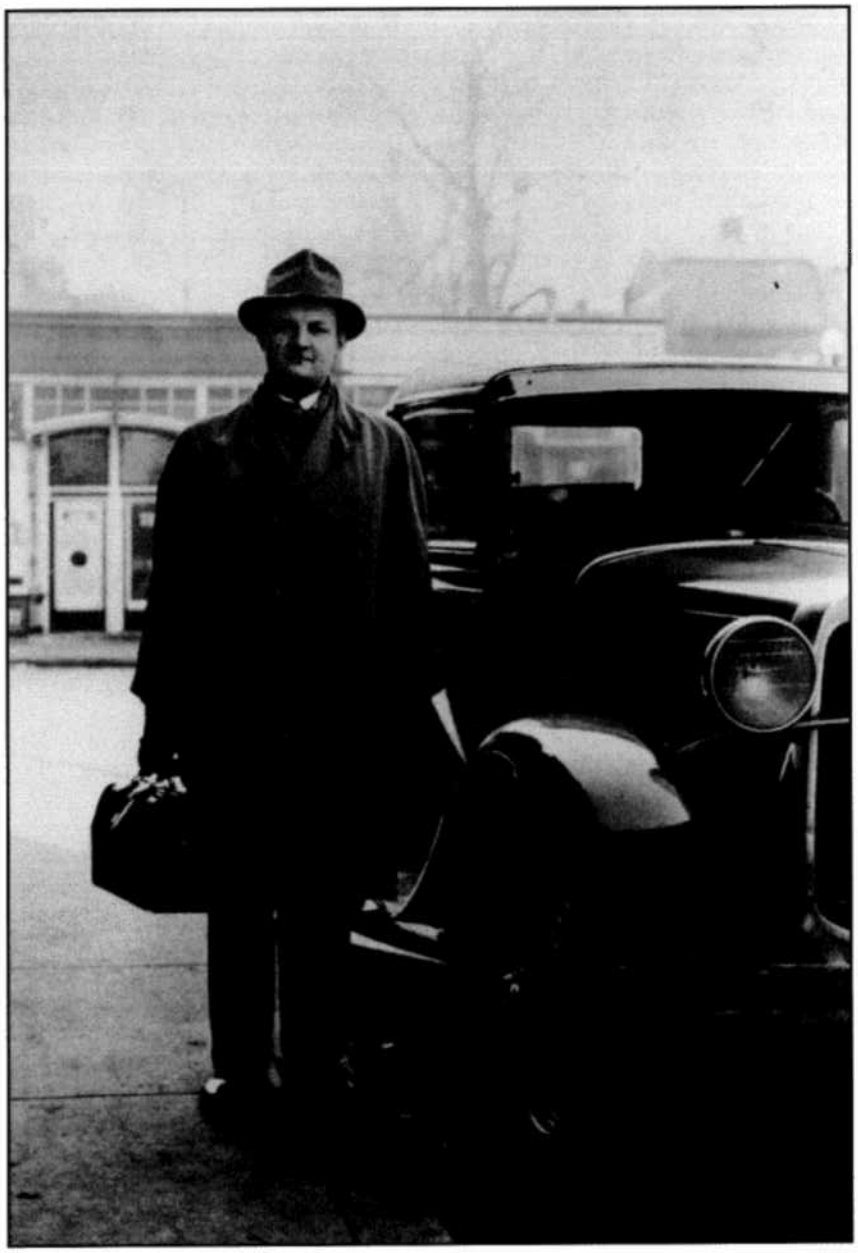
That was 50 years ago. I retired from general practice in Kaneohe, Oahu in 1991 but still see a few patients bedridden in their homes and I volunteer at a comprehensive health clinic one

morning a week, now 55 years with MD after my name.

What a remarkable half-century it has been, actually three-quarters of a century since I was born in 1913! I was in two world wars. As a child in the Ural mountains of imperial Russia, I remember seeing the first clear glass incandescent light bulb invented by Thomas Edison. As my physician father, my mother and younger brother, and I escaped from the Bolsheviks during the Russian revolution and arrived in Vladivostok, thanks to the American Red Cross and the American Expeditionary Force in Siberia, I remember seeing a model-T Ford car and still can smell, in my imagination, the strange odor of gasoline exhaust. In 1925, as a boy living in Kahaluu next to Libby, McNeil & Libby's huge pineapple cannery, I remember a neighbor's new Atwater-Kent, full-of-static, wireless radio. That same year I remember seeing, with wonder, a small seaplane circling over our Kahaluu house and landing in Kaneohe Bay, then taking off to windward. The age of radio and of airplanes had begun. The age of black-and-white television ensued, followed by color. Much earlier, we attended movies from "flickers" to full color. Jet engines on planes supplanted the propellers and finally the electronic age came into being, the changes and the "new" things coming ever faster and faster. Finally, just as I reached retirement age, the practice of medicine changed and I was glad that I would not have to be a part of the provider/consumer, bottom-line-business, third-party-intervenor bureaucracy that it seems the healing profession will have to submit to, unless rescued by organized medicine.

Biaxin, the latest? Never! The bacteria are gaining on us and the viruses are thriving.

Aloha to those dedicated physicians who follow in our footsteps, healers *per primum*, businessmen and women perforce. *Auwe!*



John Iorwerth Frederick Reppun, MD
Ready to deliver the first baby, Boston 1939